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10/529,713	03/31/2006	Hideyuki Yasuno	18201-003US1 RCJA0213P-US	4470
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary

Application No.

10/529,713

Applicant(s)

YASUNO ET AL.

Examiner

SUCHIRA PANDE

Art Unit

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 March 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 6-17, 19 and 24-29 is/are pending in the application.
- 4a) Of the above claim(s) 6-15 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 16, 17, 19 and 24-29 is/are rejected.
- 7) ☒ Claim(s) 1 and 24 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/888)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Claim Status

1. Amendment filed on March 27, 2009 is acknowledged. Applicant has amended claims 1, 16, 19 and 24; cancelled claims 2-5, 18, 20-23; withdrawn claims 6-15; and added new claims 25-29. Currently claims 1, 16, 17, 19, and 24-29 are active and will be examined in this action.

Response to Arguments

Re 102 rejection of claims 1-2, 4 and 5 over Luo et al.

2. Applicant has cancelled claims 2, 4 and 5. Applicant's arguments with respect to claim 1 have been considered but are moot in view of the new ground(s) of rejection. Claim 1 has been amended to include SEQ ID NO 1. Previously cited art Luo et al. does not teach sequence of SEQ ID NO 1. Therefore previously cited rejection of claim 1 over Luo et al. is being withdrawn. New art is being cited that teaches all aspects of amended claim 1.

Re 102 rejection of claims 1-3 over Marsh et al.

3. Applicant has cancelled claims 2-3. Applicant's arguments with respect to claim 1 have been considered but are moot in view of the new ground(s) of rejection. Claim 1 has been amended to include SEQ ID NO 1. Previously cited art does teach sequence of a region that comprises sequence of SEQ ID NO 1. However the currently amended claim is claiming an oligo which consists of SEQ ID NO 1. Therefore previously cited rejection of claim 1 over Marsh et al. is being withdrawn. New art is being cited that teaches all aspects of amended claim 1.

Re 103 rejection of claims 16 and 18 over Marsh et al. in view of Luo et al. and

Stratagene 1988 catalog.

4. Claim 18 is cancelled. Amended claim 16 requires two oligos consisting of specified SEQ ID NOs. Both Marsh et al. and Luo et al. teach the sequence comprising claimed SEQ IDs. Hence rejection of claims 16 over previously cited is being withdrawn. New art is being cited that teaches the changed scope of the instant claims.

Re 103 rejection of remaining claims 17, 19, 24 over primary references Marsh et al. or

Luo et al. in view of appropriate secondary references

5. Since both primary references Marsh et al. and Luo et al. have been withdrawn accordingly the 103 rejections over either of these references further in view of appropriate secondary references is no longer valid and is being withdrawn.

Claim Objections

6. Claims 1 and 24 are objected to because of the following informalities: Claims 1 and 24 were amended. These amended claims are directed to oligonucleotides of SEQ ID No 1 and SEQ ID No 2 respectively. In the current recitation the claims lack the word "isolated". Conventionally such claims read as follows:

—An isolated oligonucleotide, the ----".

Appropriate correction is required.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Independent claims 1, 16, 19 and 28 all recite oligonucleotide of SEQ ID NO 1. This aspect of all of the above claims is being considered together in claim 1. Similarly Independent claims 24, 16 and 19 all recite oligonucleotide of SEQ ID NO 2. This aspect of all of the above claims is being considered together in claim 24. Aspects of claims that are different are addressed separately.

10. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Marsh et al. (1999) Genomics 58 (3) 310-312 in view of Buck et al. (1999) Biotechniques 27:528-536.

Regarding claim 1, Marsh et al. teach sequence of a region comprising the claimed sequence of the oligonucleotide identified by SEQ ID NO 1. See alignment shown below where portion of the sequence of 140 bases taught by Marsh et al. (nt 66 to 92) shows 100 % identity to oligo of claimed SEQ ID NO 1:

TITLE Ethnic variation in the thymidylate synthase enhancer region
polymorphism among Caucasian and Asian populations

```
JOURNAL    Genomics 58 (3), 310-312 (1999)

Query Match      100.0%;   Score 27;   DB 5;   Length 140;
Best Local Similarity 100.0%;   Pred. No. 1e+02;
Matches 27;   Conservative 0;   Mismatches 0;   Indels 0;   Gaps
0;

Qy          1 CTTGGCCTGCCTCCGTCCCGCCGCGCC 27   SEQ ID No.1
            |||
Db          66 CTTGGCCTGCCTCCGTCCCGCCGCGCC 92
```

Thus Marsh et al. teach sequence of the region encompassing the claimed oligo.

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention was made to have used the method of Buck et al. to design the design the oligonucleotide claimed in instant application as SEQ ID No 1 using the teaching of sequences of thymidylate synthetase enhancer region taught by Marsh et al. as the starting point.

In the recent court decision *KSR International Co. v. Teleflex Inc.*, 82 127 SCt 1727 (2007), the U.S. Supreme Court determined that if the combination of the claimed elements was "obvious to try" by a person of ordinary skill, this might show that such a combination was obvious under §103. Regarding "obvious to try", the Court stated:

"A person of ordinary skill is also a person of ordinary creativity, not an automaton. The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." *Id.*, at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103."

The sequence of Thymidylate synthase enhancer region/organism is taught to one of ordinary skill by prior art and one of ordinary skill in the art is capable of

designing primer/probes useful for amplifying a given region of any nucleic acid whose sequence is known and detecting it using FRET technique. PCR amplification is currently one of the fastest, cheapest way of detecting presence of any given nucleic acid, provided some information is available based on which amplification primers flanking the region to be amplified can be designed. Similarly quantitative FRET detection is very sensitive method capable of detecting even one molecule.

Since the claimed primers/probes simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the Thymidylate synthase enhancer gene/region/genome and concerning which a biochemist of ordinary skill would attempt to obtain suitable primers flanking the region of interest, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing

analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2).” Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Thus regarding independent claims 1, 16, 19 and 28 Marsh et al. in view of Buck et al. teach an oligonucleotide, the sequence of which consists of SEQ ID NO:1.

11. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Luo et al. (2002) Biochemical Genetics vol. 40. Nos 1 / 2, pp. 41-51 in view of Buck et al. (1999) Biotechniques 27:528-536.

Regarding claim 24, Luo et al. teach sequence of a region comprising the claimed sequence of the oligonucleotide identified by SEQ ID NO 2. See alignment shown below where portion of the sequence of 165 bases taught by Luo et al. (nt 85 to 134 shows 98 % homology to oligo of claimed SEQ ID NO 2. At position 125 of the sequence taught by Luo et al. the sequence does not match the claimed oligo sequence.

```
RESULT 3
AF279907
LOCUS      AF279907                165 bp    DNA        linear    PRI 14-OCT-
2005
DEFINITION Homo sapiens thymidylate synthase (TSER) gene, TSER-2 allele,
partial sequence.
ACCESSION  AF279907
VERSION    AF279907.1   GI:12802219
KEYWORDS   .
SOURCE     Homo sapiens (human)
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Art Unit: 1637

ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
Catarrhini; Hominidae; Homo.

REFERENCE 1 (bases 1 to 165)

AUTHORS Luo,H.R., Lu,X.M., Yao,Y.G., Horie,N., Takeishi,K., Jorde,L.B.
and Zhang,Y.P.

TITLE Length polymorphism of thymidylate synthase regulatory region in
Chinese populations and evolution of the novel alleles

JOURNAL Biochem. Genet. 40 (1-2), 41-51 (2002)

PUBMED 11989786

REFERENCE 2 (bases 1 to 165)

AUTHORS Luo,H.-R., Lu,X.-M., Yao,Y.-G. and Zhang,Y.-P.

TITLE Direct Submission

JOURNAL Submitted (18-JUN-2000) Laboratory of Cellular and Molecular
Evolution, Kunming Institute of Zoology, Chinese Academy of
Sciences, Jiaochang Donglu 32, Kunming, Yunnan 650223, China

FEATURES
Location/Qualifiers

source 1..165
/organism="Homo sapiens"
/mol_type="genomic DNA"
/db_xref="taxon:9606"
/chromosome="18"
/map="18p11.32"

gene 1..>165
/gene="TSER"
/allele="TSER-2"
/note="thymidylate synthase"

misc_feature 1..>165
/gene="TSER"
/allele="TSER-2"
/note="5' flanking region; contains two repeats"

ORIGIN

Query Match 96.8%; Score 48.4; DB 5; Length 165;
Best Local Similarity 98.0%; Pred. No. 7.8e-06;
Matches 49; Conservative 0; Mismatches 1; Indels 0; Gaps
0;

Qy 1 CGCGGAAGGGGTCTGCCACCGGCCACTTGGCCTGCCTCGGTCCCGCG 50
Db 85 CGCGGAAGGGGTCTGCCACCGGCCACTTGGCCTGCCTCGGTCCCGCG 134

Thus Luo et al. teach sequence of the region encompassing the claimed oligo.

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention was made to have used the method of Buck et al. to design the design the oligonucleotide claimed in instant application as SEQ ID No 2 using the

teaching of sequences of thymidylate synthetase enhancer region taught by Luo et al. as the starting point. One of ordinary skill in the art knows oligo containing one internal mismatch will still hybridize to the sequences of thymidylate synthetase enhancer region.

In the recent court decision *KSR International Co. v. Teleflex Inc.*, 82 127 S.Ct 1727 (2007), the U.S. Supreme Court determined that if the combination of the claimed elements was "obvious to try" by a person of ordinary skill, this might show that such a combination was obvious under §103. Regarding "obvious to try", the Court stated:

"A person of ordinary skill is also a person of ordinary creativity, not an automaton. The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." *Id.*, at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103."

The sequence of Thymidylate synthase enhancer region/organism is taught to one of ordinary skill by prior art and one of ordinary skill in the art is capable of designing primer/probes useful for amplifying a given region of any nucleic acid whose sequence is known and detecting it using FRET technique. PCR amplification is currently one of the fastest, cheapest way of detecting presence of any given nucleic acid, provided some information is available based on which amplification primers flanking the region to be amplified can be designed. Similarly quantitative FRET detection is very sensitive method capable of detecting even one molecule.

Since the claimed primers/probes simply represent structural homologs, which

are derived from sequences suggested by the prior art as useful for primers of the Thymidylate synthase enhancer gene/region/genome and concerning which a biochemist of ordinary skill would attempt to obtain suitable primers flanking the region of interest, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Thus regarding independent claims 24, 16 and 19 Luo et al. in view of Buck et al. teach an oligonucleotide, the sequence of which consists of SEQ ID NO:2.

12. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Marsh et al. (1999) Genomics 58 (3) 310-312; Luo et al. (2002) Biochemical Genetics vol. 40. Nos 1/2 pp. 41-51; Buck et al. (1999) Biotechniques 27:528-536 and Stratagene 1988 catalog.

Regarding claim 16, Marsh et al. and Buck et al. teach (a) a first oligonucleotide, the sequence of which consists of SEQ ID NO: 1 or the exact complementary sequence thereof (see details in claim 1 above).

Regarding claim 16, Luo et al. and Buck et al. teach (b) a second oligonucleotide, the sequence of which consists of SEQ ID NO:2 or the exact complementary sequence thereof (see details in claim 24 above).

Regarding claim 16, none of the above references Marsh et al.; Luo et al. or Buck et al. teach a kit format.

Regarding claim 16, Stratagene catalog 1988 teaches use of kit format. Stratagene 1988 teaches kits for gene characterization and they also have kit for hybridizing nucleic acids.

It would have been prima facie obvious to one of ordinary skill in the art to package the oligonucleotides taught by Marsh et al.; Luo et al. and Buck et al. for determination of number of polymorphic repeats present in the regulatory portion of thymidylate synthase gene in form of kit as taught by Stratagene, at the time the invention was made. The motivation to do so is provided to one of ordinary skill by

Stratagene catalog that states "In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control.----Stratagene tests all of the components included in each kit in concert, and demonstrates that they perform well together. This can undoubtedly save you weeks of costly and frustrating trouble --shooting."

13. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Marsh et al. Luo et al.; Buck et al. and Stratagene 1988 catalog as applied to claim 16 above further in view of Dobrowolski et al. US PG pub 2004/0219557 A1).

Regarding claim 17, Marsh et al. Luo et al.; Buck et al. and Stratagene 1988 catalog teaches the kit of claim 16.

Regarding claim 17, Marsh et al. Luo et al.; Buck et al. and Stratagene 1988 catalog do not teach the downstream end of the second oligonucleotide is labeled with FITC, and the upstream end of the first oligonucleotide is labeled with the fluorescent dye RED640 or RED705.

Regarding claim 17, Dobrowolski et al. et al. teaches the downstream end of the second oligonucleotide is labeled with FITC, and the upstream end of the first oligonucleotide is labeled with the fluorescent dye RED640. (see page 3, par. 0023)

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the guidelines and principles taught by Dobrowolski et al. to design the oligonucleotide claimed in the instant application as primer/probes to be used for detection of insertion or deletion polymorphisms in the thymidylate synthase regulatory region present in human population as taught to one

of ordinary skill by Marsh et al. and Luo et al. The motivation to do so is provided by Dobrowolski et al. who teach FRET based detection of mutation and state " Air driven thermal cycling is fast, genotyping with fluorescent hybridization probes is simple because it involves no post-PCR manipulation, and melting peak data is easily interpreted. From isolation of DNA to data interpretation, the 5-mutation panel described here is completed in less than 2 hours. Such rapid analysis assures that second tier molecular data is reported along with the primary biochemical data. An additional benefit is that the close tube format simplifies sample tracking and is favorable for avoiding amplicon contamination in the laboratory. Data files from the Light Cycler are easily stored and may be backed up in an off-site archive rendering them safe from loss. This is an ideal situation for the newborn screening laboratory where large quantities of sensitive clinical data are generated." (see page 5 par. 0032). Based on above teaching one of ordinary skill in the art is motivated to design fluorescent probes as taught by Dobrowolski et al. to *perform FRET based polymorphism detection* using the Light Cycler system with a reasonable expectation of success.

14. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Marsh et al. (1999) Genomics 58 (3) 310-312; Luo et al. (2002) Biochemical Genetics vol. 40. Nos 1 /2 pp. 41-51; Buck et al. (1999) Biotechniques 27:528-536 in view of Stratagene 1988 catalog and further in view of Dobrowolski et al. US PG pub 2004/0219557 A1.

Regarding claim 19, Marsh et al. and Buck et al. teach (a) a first oligonucleotide, the sequence of which consists of SEQ ID NO: 1 or the exact complementary sequence thereof (see details in claim 1 above).

Regarding claim 19, Luo et al. and Buck et al. teach (b) a second oligonucleotide, the sequence of which consists of SEQ ID NO:2 or the exact complementary sequence thereof (see details in claim 24 above).

Regarding claim 19, none of the above references Marsh et al.; Luo et al. or Buck et al. teach a kit format.

Regarding claim 19, Stratagene catalog 1988 teaches use of kit format. Stratagene 1988 teaches kits for gene characterization and they also have kit for hybridizing nucleic acids.

It would have been prima facie obvious to one of ordinary skill in the art to package the oligonucleotides taught by Marsh et al.; Luo et al. and Buck et al. for determination of number of polymorphic repeats present in the regulatory portion of thymidylate synthase gene in form of kit as taught by Stratagene, at the time the invention was made. The motivation to do so is provided to one of ordinary skill by Stratagene catalog that states "In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control.----Stratagene tests all of the components included in each kit in concert, and demonstrates that they perform well together. This can undoubtedly save you weeks of costly and frustrating trouble --shooting."

Regarding claim 19, Marsh et al.; Luo et al.; Buck et al. and Stratagene catalog do not teach each of the each of the oligonucleotides being optionally labeled with a fluorescent dye.

Regarding claim 19, Dobrowolski et al. teach oligonucleotide being optionally labeled with a detectable label (see page 1 par. 0012 where use of labeled detection probe and subsequent detection using FRET is taught, thus Dobrowolski et al. teach each of the oligonucleotide being optionally labeled with a detectable fluorophore label).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the guidelines and principles taught by Dobrowolski et al. to design the oligonucleotide claimed in the instant application as primer/probes to be used for detection of insertion or deletion polymorphisms in the thymidylate synthase regulatory region present in human population as taught to one of ordinary skill by Luo et al. The motivation to do so is provided by Dobrowolski et al. who teach FRET based detection of mutation and state " Air driven thermal cycling is fast, genotyping with fluorescent hybridization probes is simple because it involves no post-PCR manipulation, and melting peak data is easily interpreted. From isolation of DNA to data interpretation, the 5-mutation panel described here is completed in less than 2 hours. Such rapid analysis assures that second tier molecular data is reported along with the primary biochemical data. An additional benefit is that the close tube format simplifies sample tracking and is favorable for avoiding amplicon contamination in the laboratory. Data files from the Light Cycler are easily stored and may be backed up in an off-site archive rendering them safe from loss. This is an ideal situation for the

newborn screening laboratory where large quantities of sensitive clinical data are generated." (see page 5 par. 0032). Based on above teaching one of ordinary skill in the art is motivated to design fluorescent probes as taught by Dobrowolski et al. to *perform FRET based polymorphism detection* using the Light Cycler system with a reasonable expectation of success.

15. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Marsh et al. and Buck et al. as applied to claim 1 above further in view of Dobrowolski et al. US PG pub 2004/0219557 A1.

Regarding claim 25, Marsh et al. and Buck et al. teach the oligonucleotide of claim 1 but do not teach wherein the oligonucleotide is labeled with a detectable label.

Regarding claim 25, Dobrowolski et al. teach wherein the oligonucleotide is labeled with a detectable label (see page 1 par. 0012 where use of labeled detection probe and subsequent detection using FRET is taught, thus Dobrowolski et al. teach wherein the oligonucleotide is labeled with a detectable label).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the guidelines and principles taught by Dobrowolski et al. to design the oligonucleotide claimed in the instant application as primer/probes to be used for detection of insertion or deletion polymorphisms in the thymidylate synthase regulatory region present in human population as taught to one of ordinary skill by Luo et al. The motivation to do so is provided by Dobrowolski et al. who teach FRET based detection of mutation and state " Air driven thermal cycling is fast, genotyping with fluorescent hybridization probes is simple because it involves no post-PCR

manipulation, and melting peak data is easily interpreted. From isolation of DNA to data interpretation, the 5-mutation panel described here is completed in less than 2 hours. Such rapid analysis assures that second tier molecular data is reported along with the primary biochemical data. An additional benefit is that the close tube format simplifies sample tracking and is favorable for avoiding amplicon contamination in the laboratory. Data files from the Light Cycler are easily stored and may be backed up in an off-site archive rendering them safe from loss. This is an ideal situation for the newborn screening laboratory where large quantities of sensitive clinical data are generated." (see page 5 par. 0032). Based on above teaching one of ordinary skill in the art is motivated to design fluorescent probes as taught by Dobrowolski et al. to *perform FRET based polymorphism detection* using the Light Cycler system with a reasonable expectation of success.

16. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Luo et al. and Buck et al. as applied to claim 24 above further in view of Dobrowolski et al. US PG pub 2004/0219557 A1.

Regarding claim 26, Luo et al. and Buck et al. teach the oligonucleotide of claim 24 but do not teach wherein the oligonucleotide is labeled with a detectable label.

Regarding claim 26, Dobrowolski et al. teach wherein the oligonucleotide is labeled with a detectable label (see page 1 par. 0012 where use of labeled detection probe and subsequent detection using FRET is taught, thus Dobrowolski et al. teach wherein the oligonucleotide is labeled with a detectable label).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the guidelines and principles taught by Dobrowolski et al. to design the oligonucleotide claimed in the instant application as primer/probes to be used for detection of insertion or deletion polymorphisms in the thymidylate synthase regulatory region present in human population as taught to one of ordinary skill by Luo et al. The motivation to do so is provided by Dobrowolski et al. who teach FRET based detection of mutation and state " Air driven thermal cycling is fast, genotyping with fluorescent hybridization probes is simple because it involves no post-PCR manipulation, and melting peak data is easily interpreted. From isolation of DNA to data interpretation, the 5-mutation panel described here is completed in less than 2 hours. Such rapid analysis assures that second tier molecular data is reported along with the primary biochemical data. An additional benefit is that the close tube format simplifies sample tracking and is favorable for avoiding amplicon contamination in the laboratory. Data files from the Light Cycler are easily stored and may be backed up in an off-site archive rendering them safe from loss. This is an ideal situation for the newborn screening laboratory where large quantities of sensitive clinical data are generated." (see page 5 par. 0032). Based on above teaching one of ordinary skill in the art is motivated to design fluorescent probes as taught by Dobrowolski et al. to *perform FRET based polymorphism detection* using the Light Cycler system with a reasonable expectation of success.

17. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Marsh et al. Luo et al.; Buck et al.; Stratagene 1988 catalog; Dobrowolski et al. as applied to

claim 17 above further in view of Pals et al. (2001) J. Biochem. Biophys. Methods 47: pp 121-129 (newly cited).

Regarding claim 27, Marsh et al. Luo et al.; Buck et al.; Stratagene 1988 catalog; Dobrowolski et al. teach kit of claim 17, and also teach wherein the upstream end of the first oligonucleotide is labeled with the fluorescent dye RED640. But they do not teach use of fluorescent dye RED705.

Regarding claim 27, Pals et al. teach wherein the upstream end (5' end) of the first oligonucleotide is labeled with the fluorescent dye RED705 (see page 121 abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use appropriate fluorescent dye (RED705 or RED640) to label the oligos based on the experimental design. SEE MPEP 2144.06 Art Recognized Equivalence for the Same Purpose [R-6] < SUBSTITUTING EQUIVALENTS KNOWN FOR THE SAME PURPOSE. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

18. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Marsh et al. (1999) Genomics 58 (3) 310-312 ; Buck et al. (1999) Biotechniques 27:528-536 in view of Stratagene 1988 catalog.

Regarding claim 28, Marsh et al. in view of Buck et al. teach

(i) the oligonucleotide of claim 1 (see details above in claim 1) and

(ii) a second oligonucleotide that hybridizes to the region adjacent to the 5' side of the oligonucleotide of claim 1. (Marsh et al. teach the tandem repeat sequence in a thymidylate synthase promoter enhancer region (see page 310 abstract). The oligo of claim 1 is part of this region taught by Marsh et al. The upstream sequence on the 5' side of the oligonucleotide of claim 1 in the thymidylate synthase promoter enhancer region is taught by Marsh et al.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to design a second oligonucleotide using the method of Buck et al. such that this second oligonucleotide hybridizes to the region adjacent to the 5' side of the oligonucleotide of claim 1 using the thymidylate synthase promoter enhancer region taught by Marsh et al. as starting point.

In the recent court decision *KSR International Co. v. Teleflex Inc.*, 82 127 SCt 1727 (2007), the U.S. Supreme Court determined that if the combination of the claimed elements was "obvious to try" by a person of ordinary skill, this might show that such a combination was obvious under §103. Regarding "obvious to try", the Court stated:

"A person of ordinary skill is also a person of ordinary creativity, not an automaton. The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." *Id.*, at 289 (internal quotation marks omitted). When there

is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103."

The sequence of Thymidylate synthase enhancer region/organism is taught to one of ordinary skill by prior art and one of ordinary skill in the art is capable of designing primer/probes useful for amplifying a given region of any nucleic acid whose sequence is known and detecting it using FRET technique. PCR amplification is currently one of the fastest, cheapest way of detecting presence of any given nucleic acid, provided some information is available based on which amplification primers flanking the region to be amplified can be designed. Similarly quantitative FRET detection is very sensitive method capable of detecting even one molecule.

Since the claimed primers/probes simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the Thymidylate synthase enhancer gene/region/genome and concerning which a biochemist of ordinary skill would attempt to obtain suitable primers flanking the region of interest, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see

page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Regarding claim 28, neither Marsh et al. nor Buck et al. teach use of Kit format.

Regarding claim 28, Stratagene catalog 1988 teaches use of kit format. Stratagene 1988 teaches kits for gene characterization and they also have kit for hybridizing nucleic acids.

It would have been prima facie obvious to one of ordinary skill in the art to package the oligonucleotides taught by Marsh et al.; and Buck et al. for determination of number of polymorphic repeats present in the regulatory portion of thymidylate synthase gene in form of kit as taught by Stratagene, at the time the invention was made. The motivation to do so is provided to one of ordinary skill by Stratagene catalog that states "In actuality, the kit format saves money and resources for everyone by dramatically

reducing waste. 2) The other service provided in a kit is quality control.----Stratagene tests all of the components included in each kit in concert, and demonstrates that they perform well together. This can undoubtedly save you weeks of costly and frustrating trouble --shooting."

19. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Marsh et al.; Buck et al. and Stratagene 1988 catalog as applied to claim 28 above further in view of Pals et al. (2001) J. Biochem. Biophys. Methods 47: pp 121-129.

Regarding claim 29, Marsh et al.; Buck et al. and Stratagene 1988 catalog teach the kit of claim 28. They also teach the oligonucleotide of (i) and the oligonucleotide of (ii); but they do not teach wherein the 5' end of the oligonucleotide of (i) is labeled with the fluorescent dye RED640 or RED705, and the 3' end of the oligonucleotide of (ii) is labeled with the fluorescent dye FITC.

Regarding claim 29, Pals et al. teach wherein the 5' end of the oligonucleotide of (i) is labeled with the fluorescent dye RED640 or RED705 (See page 121 abstract where the 3' probes, are taught to be labeled at 5' end with LCRED 640 (wild type probe) or LCRED 705 (mutant probe)), and

the 3' end of the oligonucleotide of (ii) is labeled with the fluorescent dye FITC. (See page 121 abstract where the 5'-probe is taught to be 3' labeled with FITC).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to label the oligonucleotides (i) and (ii) of the kit of claim 28 with the pair of fluorescent dyes taught by Pals et al. The motivation to do so is provided to one of ordinary skill in the art by Pals et al. who teach use of such probes to detect

mutations in a single cell using the LightCycler™. (see whole article). They state "Dual color detection of wild type and mutant sequences in a single tube was tested on single cells. The reaction mix was prepared in reaction capillaries and a single cell, picked by micromanipulation, was added to this mix. The DNA from the cell is released during the 5-min preheating step of the PCR, using the fast start hybridization kit (Roche). Reproducible results were obtained, without the need of nested PCR. The technique is useful for microdissected tumors and, with other genes, has great potential for pre-implantation diagnosis in IVF and analysis of residual disease in cancer." (see page 121 last part of abstract).

Based on the above teachings of Pals et al. one of ordinary skill in the art has a reasonable expectation of success in being able to detect the mutations in the thymidylate synthase gene using the real time polymerase chain reaction followed by melting curve analysis using hybridization probes that are labeled with LCRED 640 or LCRED 705 (The LCRED labeled probe correspond to the 3' probe which have label at 5' end) and FITC (FITC labeled probe correspond to the 5' probe which have label at 3' end).

Conclusion

20. All claims under consideration 1, 16, 17, 19, and 24-29 are rejected over prior art.
21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUCHIRA PANDE whose telephone number is (571)272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suchira Pande
Examiner
Art Unit 1637

/Teresa E Strzelecka/

Primary Examiner, Art Unit 1637

June 22, 2009